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The Use of Sodium Amide in Organic Synthesis

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THE USE OF alkali-metal amides, especially sodium amide, in the synthesis of organic chemicals has been discussed at considerable length in the literature (*1*); but the extensive employment of these amides in research has been hindered by the difficulties encountered in making them and by their lack of stability. The recent publication (*2*) of an improved method of preparing sodium amide, with resultant greater stability, has renewed the interest in this important reagent.

The nature of sodium amide is such that it must be handled with great care. It is extremely reactive, being very similar to sodium metal, and must at all times be stored under an inert liquid; it reacts explosively with water and combines readily with oxygen. The recommended method of storage is in a wide-mouthed bottle, under a petroleum fraction such as commercial heptane.

Generally speaking, sodium amide reacts similarly to sodium hydroxide or the sodium alcoholates, but it has the distinct advantage that, in reactions involving dehydration or the formation of a sodium "salt," ammonia is formed instead of water or alcohol. The evolution of ammonia forces the reaction to completion by displacing the equilibrium to the right; it also provides a convenient indicator for the beginning and end of the reaction. Sodium amide has the advantage over sodium metal in that when it is used to replace an active hydrogen, no reduction can take place.

Sodium amide is more effective than sodium ethylate for the Claisen condensation of an ester with a ketone; benzoylacetone is obtained in 77 per cent yield by the condensation of ethyl benzoate with acetone.

A widely employed synthesis in which sodium amide is of particular value is the alkylation of ketones. The aryl alkyl ketones, in boiling benzene, react thusly—

$$ArCOCH_3 \xrightarrow{NaNH_2} ArC(=CH_2)ONa \xrightarrow{RX} ArCOCH_2R + NaX$$

The procedure may be repeated to give the trialkylated com-

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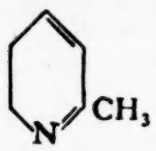
pound, each succeeding alkyl group being added more readily than the previous one. The alkyl halides may be methyl, ethyl, propyl, allyl (as second and third group only), or benzyl, but not aryl or higher alkyls.

The alkylation of simple aliphatic and alicyclic ketones, by the same procedure, leads largely to the condensation of the ketone with itself. However, the sodium "salts" of such ketones can be formed from a dilute ether solution of the ketone and sodium amide at, or below, −10° C.; the sodium "salt" may then be alkylated in the same manner as are the aryl alkyl ketones.

The 2- and 4-methyl pyridines may be alkylated in the same way as the ketones, and may also be condensed with the esters of aromatic carboxylic acids in the manner of a Claisen condensation. This is possible because, as can be seen from the structure at the left, these compounds are ketones in the ammonia system of classification.



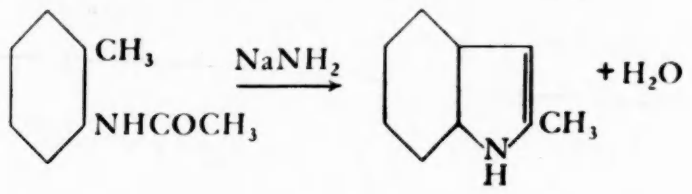
Ziegler (*3*) has developed a general method for the alkylation of nitriles that have a hydrogen atom on the carbon adjacent to the nitrile group. Thus, capronitrile is formed from acetonitrile, sodium amide, and butyl bromide, in ether. However, the conditions must be controlled carefully, for, in the presence of sodium amide, the nitriles tend to condense with themselves to form the dimeric dinitriles; or they may react with excess sodium amide to form the amidines. (This is a good method for the preparation of aromatic amidines.) Phenylacetonitrile has little tendency to undergo these side reactions and, therefore, can be alkylated very readily.

The splitting of aromatic ketones may be accomplished much more readily with sodium amide than with potassium hydroxide, merely by refluxing the reagents in benzene or toluene—

$$2RCOR' \xrightarrow{NaNH_2} RH + R'CONH_2 + R'H + RCONH_2$$

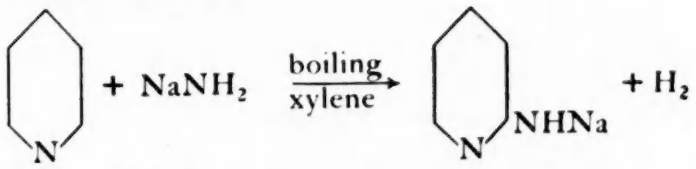
The groups R and R′ have a marked influence on the principal point of cleavage. This reaction is often valuable in determining the structure of ketones and, when it proceeds preponderantly in one direction, it may be used as a preparative method.

Sodium amide or organic derivatives of sodium amide have proved to be very effective condensing agents in certain dehydrations; the water liberated reacts immediately with the amide, so that anhydrous conditions are maintained. The most notable industrial example is the use of sodium amide in place of fused alkali in the cyclization of N-phenylglycine to indoxyl, the first step in the synthesis of indigo. In commercial practice, the sodium amide is prepared *in situ* from molten sodium and ammonia and is then diluted with fused alkali. Another reaction of this general type is—



Sodium amide is also a very effective catalyst for the aldol condensation reaction. Thus, acetone in the presence of sodium amide forms isophorone; and a mixture of citral and acetone gives pseudoionone in improved yields over those obtained by the use of mild alkalis.

The preparation of aminopyridines by the well-known Chichibabin synthesis is an important industrial use of sodium amide—



The reaction will also take place, but with more or less difficulty, when various substituted pyridines are employed. The amino group normally enters the 2 or 6 position; however, if these are blocked, it will enter the 4 position. In laboratory practice, quinoline does not work well in this synthesis; but on a commercial scale, 2-aminoquinoline may be prepared in this manner.

Aminations also occur in certain aromatic nuclei. A notable example is the piperidination of 7-meso-benzanthrenone, to give 4(1-piperidyl)-7-meso-benzanthrenone in a good yield.

Another type of synthesis in which sodium amide is employed, is the preparation of acetylenic carbinols by the Nef reaction—

$$CH_3COCH_3 + C_2H_2 \xrightarrow{NaNH_2} (CH_3)_2CC \equiv CH \quad (OH)$$

The reaction must be kept very cold to prevent self-condensation of the ketone. The acetylenic carbinols are useful intermediates for further syntheses and were used by Ruzicka and Fischer (*4*) in the preparation of phytol and products approximating vitamin A alcohol.

Sodium amide has proved to be superior to other alkaline reagents in the synthesis of acetylenes from haloethylenes because of the fact that polymerization is decreased.

It has recently been reported that alkylamines may be prepared by reacting alkyl halides and sodium amide in liquid ammonia. However, with sodium amide in inert solvents, alkyl halides eliminate hydrogen chloride and form ethylenes; the reaction is often accompanied by simultaneous isomerization.

Such hydrocarbons as indene and fluorene possess active methylene groups that will form sodium "salts," with sodium amide. This property has been used as a means of separating these compounds from the crude fractions obtained by distillation of drip oil or coal tar. The "salts" may then be hydrolyzed to the hydrocarbons or used as such.

There are numerous other reactions involving sodium amide and organic compounds, but they have not been discussed here because they are of more theoretical than practical interest.

NOTE—

This article is published because of the general interest in the subject matter presented, and the value of sodium amide as a reagent in certain organic syntheses. The compound is not included in the Eastman list of chemicals; neither is there anticipation that it will be offered in the future because of the hazards involved in storage and handling, and the restrictions on shipment.

Literature Cited

(*1*) *Chem. Rev.* **12,** 43 (1933); **20,** 413 (1937).
(*2*) *Org. Syntheses*, **20,** 86 (1940).
(*3*) Additional work of Ziegler was discussed in *Synthetic Org. Chemicals*, **12:** No. 4 (1940).
(*4*) Ruzicka and Fischer, *Helv. Chim. Acta*, **17,** 633 (1934).

Vacuum Distillation in Organic Research

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EVERY YEAR organic chemists struggle with larger molecules whose size makes more difficult the task of purifying mixtures of these molecules by distillation. That reasonable separations are secured from mobile liquids boiling in a laboratory flask is a tribute to the tremendous turbulence that is produced by boiling, and the rapid diffusion that occurs in mobile solutions. The desired molecules reach the surface far more rapidly than their vapor is carried away. However, when materials of high molecular weight are being handled, ebulient distillation cannot be employed for fear of decomposition and the situation is completely altered. The speed of distillation is then limited by the time taken for the molecules to reach the surface.

The old-fashioned Claisen flask, condenser, and water vacuum pumps have given place to flasks with wider necks and larger side arms, and to more efficient mechanical vacuum pumps. Now the neck and side arm are being supplanted by the short-path, or molecular, still; and this development is taking place from the "pot still," through the falling-film still, to the centrifugal still wherein the distilland is spread so thin

that no molecule is more than a thousand molecular lengths from the evaporating surface.

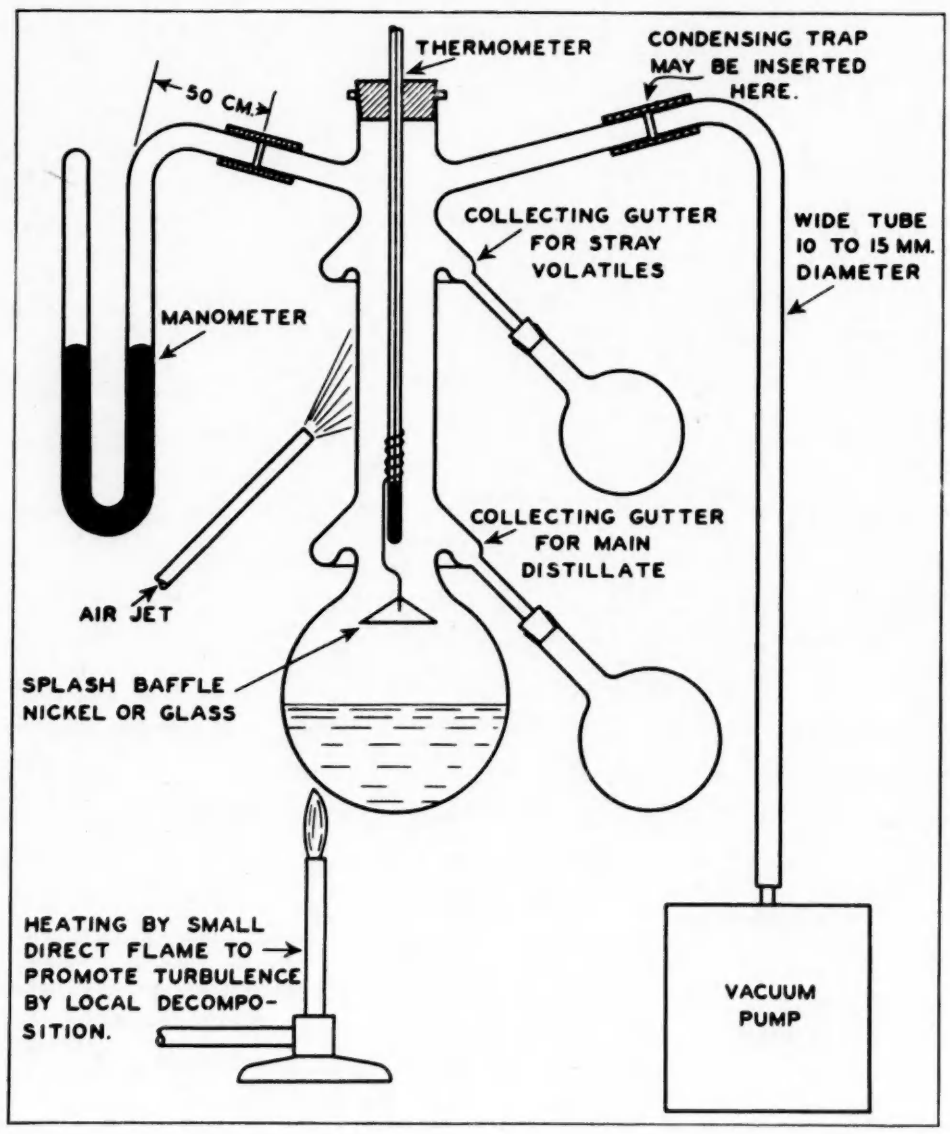
It has been found that with these stills the improvement in performance is not only a result of the large area that the distilland covers, but also of the turbulence and thinness of the layer. This focuses attention on the fact that only the distilling surface is taking part in the act of distillation. All of the substance that is not in the surface is waiting its turn to come to the surface where the volatile molecules will have a chance to escape. Furthermore, all of those volatile molecules that do not have the requisite thermal energy in the millionth of a second in which they happen to be in the surface will have to be brought there again.

As a generalization, assume that the depth of a liquid in a flask is 5 cm., that the molecules to be collected in the receiver are 5 A long, and that the time of collection will be 1 hour. The surface must be renewed ten million times during this period if every molecule is to have a chance to escape. If only one-half of the molecules, because of momentary lack of energy, are able to avail themselves of that opportunity, the surface must be renewed twenty million times.

The use of carrier gas to facilitate distillation is well known. What is not so widely appreciated is that the gas is often promoting distillation by stirring the distilland rather than by carrying the distillate toward the condenser. The gas may actually be repressing evaporation, because it has increased the over-all pressure in the still.

Many chemists have experienced a complete cessation of distillation only to find that a burst of vapor can be sent to the receiver by giving the flask a vigorous shake. Actually, the contents of the flask have become covered with an invisible skin, similar to that on a cup of cocoa, and it is only by continually breaking up this skin of molecules that cannot evaporate that it is possible to free the surface for molecules that can. Therefore, before abandoning the convenient Claisen flask in favor of the short-path still, the chemist should try the expedient of vigorously stirring the contents of his present apparatus.

The stirring may be accomplished by an external shaker or an internal propeller; or by inducing local decomposition and evolution of gas through application of a small naked flame. The flask should have a short, wide neck and a splash guard below the thermometer. A convenient arrangement is depicted in the diagram below.


THERMOMETER
CONDENSING TRAP MAY BE INSERTED HERE.
50 CM.
COLLECTING GUTTER FOR STRAY VOLATILES
WIDE TUBE 10 TO 15 MM. DIAMETER
MANOMETER
COLLECTING GUTTER FOR MAIN DISTILLATE
AIR JET
SPLASH BAFFLE NICKEL OR GLASS
HEATING BY SMALL DIRECT FLAME TO PROMOTE TURBULENCE BY LOCAL DECOMPOSITION.
VACUUM PUMP